Amendments to the Claims

This listing of claims replaces all prior versions and listings of claims in the application.

Listing of Claims

1. (Currently Amended) A method for preparing a conjugate comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), the method comprising reacting at least one functional group A of the polymer or the derivative thereof with at least one functional group Z of the protein and thereby forming a covalent linkage, wherein Z is selected from the group consisting of an amino group, a thiol group, an aldehyde group and a keto group, and

- wherein, in case Z is an aldehyde group or a keto group, A comprises an amino group forming said linkage with Z, or
- wherein, in case Z is an amino group, A is selected from the group consisting of a reactive carboxy group and an aldehyde group, a keto group or a hemiacetal group,

-- wherein, in case A is an aldehyde group, a keto group or a hemiacetal group, the method further comprises introducing A in the polymer to give a polymer derivative

--- by reacting the polymer with an at least bifunctional compound, one functional group of which reacts with the polymer and at least one other functional group of which is an aldehyde group, a keto group or a hemiacetal group, or is a functional group which is further chemically modified to give an aldehyde group, a keto group or a hemiacetal group, or

--- by oxidizing the polymer to give at least one~~, in particular at least two~~ aldehyde ~~groups~~ group, or

-- wherein, in case A is a reactive carboxy group, the method further comprises introducing A in the polymer to give a polymer derivative

--- by selectively oxidizing the polymer at its reducing end and activating

the resulting carboxy group, or

--- by reacting the polymer at its non-oxidized reducing end with a carbonic diester, or

- wherein, in case Z is a thiol group, A comprises

-- a maleimido group or

-- a halogenacetyl group

forming said linkage with Z.

2. (Original) The method as claimed in claim 1 wherein the hydroxyalkyl starch is hydroxyethyl starch.

3. (Currently Amended) The method as claimed in claim 2 wherein the hydroxyethyl starch has a molecular weight of from 2 to 200 kD~~, preferably of from 4 to130 kd, more preferably of from 4 to 70 kD~~.

4. (Currently Amended) The method as claimed in ~~any of claims 1 to 3~~ claim 1, wherein Z is an aldehyde group or a keto group.

5. (Original) The method as claimed in claim 4, wherein the aldehyde group or the keto group is located in a carbohydrate side chain of the protein and/or at the N-terminal group of the protein.

6. (Original) The method as claimed in claim 5, further comprising oxidizing the carbohydrate side chain of the protein and/or oxidizing the N-terminal group of the protein to give the aldehyde group or keto group.

7. (Original) The method as claimed in claim 6, wherein the oxidation reaction is carried out enzymatically or using a periodate, in each case, if necessary, after having removed a terminal sialic acid.

8. (Currently Amended) The method as claimed in ~~any of claims 4 to 7~~ claim 4, further comprising reacting the polymer at its non-oxidized reducing end with an at least

bifunctional linking compound comprising a functional group capable of reacting with the non-oxidized reducing end of the polymer and a group A, prior to the reaction of the polymer derivative comprising A and the protein comprising Z.

9. (Currently Amended) The method as claimed in ~~any of claims 4 to 8~~ claim 4, wherein A is an aminooxy group or a hydrazido group.

10. (Currently Amended) The method as claimed in claim 8 ~~or 9~~, wherein the at least bifunctional linking compound is a homobifunctional compound.

11. (Original) The method as claimed in claim 10, wherein the homobifunctional compound comprises two aminooxy groups.

12. (Original) The method as claimed in claim 11, wherein the homobifunctional compound is O-[2-(2-aminooxy-ethoxy)-ethyl] hydroxyl amine.

13. (Currently Amended) The method as claimed in ~~any of claims 8 to 12~~ claim 8, wherein the reaction of the polymer with the at least bifunctional linking compound is carried out in an aqueous medium.

14. (Currently Amended) The method as claimed in ~~any of claims 11 to 13~~ claim 11, wherein the reaction of the polymer with the at least bifunctional linking compound leads to an oxime linkage and/or an oxyamino linkage.

15. (Currently Amended) The method as claimed in ~~any of claims 1 to 3~~ claim 1, wherein Z is an amino group.

16. (Original) The method as claimed in claim 15, further comprising selectively oxidising the polymer at its reducing end and reacting the oxidised polymer with N, N'-disuccinimidyl carbonate at its oxidised reducing end to give a polymer derivative comprising the reactive carboxy group A.

17. (Original) The method as claimed in claim 15, further comprising reacting at least one hydroxy group of the polymer whose reducing end is not oxidised, with a carbonic diester to give the reactive carboxy group A.

18. (Original) The method as claimed in claim 17, wherein the carbonic diester is a symmetrical diester.

19. (Currently Amended) The method as claimed in claim 17 ~~or 18~~, wherein the alcohol component of the ester is selected from the group consisting of N-hydroxy succinimide, sulfonate N-hydroxy succinimide, N-hydroxy benzotriazole, and nitro-or halogen-substituted phenols.

20. (Original) The method as claimed in claim 19, wherein the halogen-substituted phenol is selected from the group consisting of nitrophenol, dinitrophenol, trichlorophenol, trifluorophenol, pentachlorophenol, and pentafluorophenol.

21. (Currently Amended) The method as claimed in ~~any of claims 17 to 20~~ claim 17, wherein the reaction of the at least one hydroxy group of the polymer whose reducing end is not oxidised, with the carbonic diester to give a reactive ester group A is carried out in an anhydrous aprotic polar solvent.

22. (Original) The method as claimed in claim 21, wherein the solvent is dimethyl acetamide, dimethyl formamide or a mixture thereof.

23. (Original) The method as claimed in claim 15, wherein A is an aldehyde group, a keto group or a hemiacetal group, the method further comprising reacting the polymer with a functional group M of an at least bifunctional compound to give a polymer derivative, the at least bifunctional compound further comprising at least one other functional group Q which is the aldehyde group, keto group or hemiacetal group A.

24. (Original) The method as claimed in claim 23, wherein M comprises an amino group.

25. (Original) The method as claimed in claim 23, wherein A is an aldehyde group, keto group or hemiacetal group, the method further comprising reacting the polymer with a functional group M of an at least bifunctional compound to give a polymer derivative, the at least bifunctional compound further comprising at least one other functional group Q which is not an aldehyde group, keto group or hemiacetal group, the method further comprising reacting the functional group Q with at least one suitable compound to give the polymer derivative comprising the aldehyde group, keto group or hemiacetal group A.

26. (Original) The method as claimed in claim 24, wherein M and Q comprise an amino group.

27. (Currently Amended) The method as claimed in claim 25 ~~or 26~~, wherein the at least one suitable compound comprises a carboxy group and an aldehyde group, keto group or hemiacetal group.

28. (Original) The method as claimed in claim 27, wherein the at least one suitable compound is formylbenzoic acid or 4-(4-formyl-3,5-dimethoxyphenoxy) butyric acid.

29. (Currently Amended) The method as claimed in claim 25 ~~or 26~~, wherein M comprises an amino group and Q comprises a beta hydroxy amino group.

30. (Original) The method as claimed in claim 29, wherein the polymer is reacted at its oxidized reducing end with a functional group M of an at least bifunctional compound.

31. (Original) The method as claimed in claim 29, further comprising oxidizing the betahydroxyamino group to give the aldehyde group.

32. (Original) The method as claimed in claim 31, wherein the oxidation reaction is carried out using a periodate.

33. (Currently Amended) The method as claimed in claim 15, wherein the polymer is subjected to a ring-opening oxidation reaction using a periodate to give a polymer derivative having at least one~~, in particular at least two~~ aldehyde ~~groups~~ group A.

34. (Currently Amended) The method as claimed in ~~any of claims 23 to 33~~ claim 23, wherein the reaction of the polymer or the polymer derivative with the protein is a reductive amination.

35. (Original) The method as claimed in claim 34, wherein the reductive amination is carried out in the presence of $NaCNBH_3$.

36. (Currently Amended) The method as claimed in claim 34 ~~or 35~~, wherein the reductive amination is carried out at a pH of 7 or less.

37. (Original) The method as claimed in claim 36, wherein the pH is 6 or less.

38. (Currently Amended) The method as claimed in ~~any of claims 34 to 37~~ claim 34, wherein the reductive amination is carried out at a temperature of from 0 to 25°C.

39. (Currently Amended) The method as claimed in ~~any of claims 34 to 38~~ claim 34, wherein the reductive amination is carried out in an aqueous medium.

40. (Currently Amended) The method as claimed in ~~any of claims 1 to 3~~ claim 1, wherein Z is a thiol group.

41. (Original) The method as claimed in claim 40, wherein A comprises a halogenacetyl group, the method further comprising reacting the polymer at its optionally oxidized reducing end with an at least bifunctional compound having at least two functional groups each comprising an amino group to give a polymer derivative having at least one functional group comprising an amino group, the method further comprising reacting the polymer derivative with a monohalogen-substituted acetic acid and/or a reactive monohalogen-substituted acetic acid derivative.

42. (Original) The method as claimed in claim 41, wherein the halogen is Br or I.

43. (Currently Amended) The method as claimed in claim 41 ~~or 42~~, wherein the at least bifunctional compound is a diaminoalkane having from 2 to 10 carbon atoms.

44. (Currently Amended) The method as claimed in claim 41 ~~or 42~~, wherein the at least bifunctional compound is adiaminopolyethylene glycol having from 1 to 5 alkylene units.

45. (Currently Amended) The method as claimed in any of claims 41 ~~to 44~~, wherein the polymer is reacted with the at least bifunctional compound at its oxidized reducing end.

46. (Currently Amended) The method as claimed in ~~any of claims 41 to 45~~ claim 41, wherein the polymer derivative comprising the halogenacetyl group is reacted with the protein in the presence of a solvent comprising a mixture of dimethyl formamide and water.

47. (Original) The method as claimed in claim 40, wherein A comprises a maleimido group, the method further comprising reacting the polymer at its optionally oxidized reducing end with an at least bifunctional compound comprising a functional group U capable of reacting with the optionally oxidised reducing end, the at least bifunctional compound further comprising a functional group W capable of being chemically modified to give a maleimido group, the method further comprising chemically modifying the functional group W to give a maleimido group.

48. (Original) The method as claimed in claim 47, wherein U comprises an amino group.

49. (Currently Amended) The method as claimed in claim 47 ~~or 48~~, wherein W comprises an amino group.

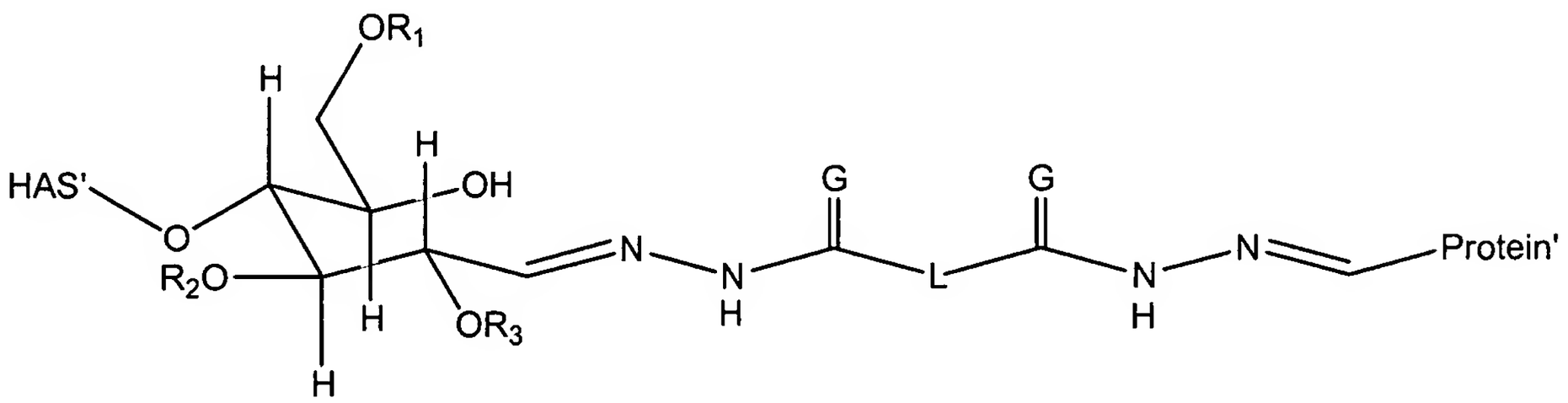
50. (Currently Amended) The method as claimed in ~~any of claims 47 to 49~~ claim 47, wherein the polymer derivative comprising W is reacted with an at least bifunctional compound comprising a functional group capable of being reacted with W and further comprising a maleimido group.

51. (Original) The method as claimed in claim 50, wherein the at least bifunctional compound is N-(alpha-maleimidoacetoxy) succinimide ester.

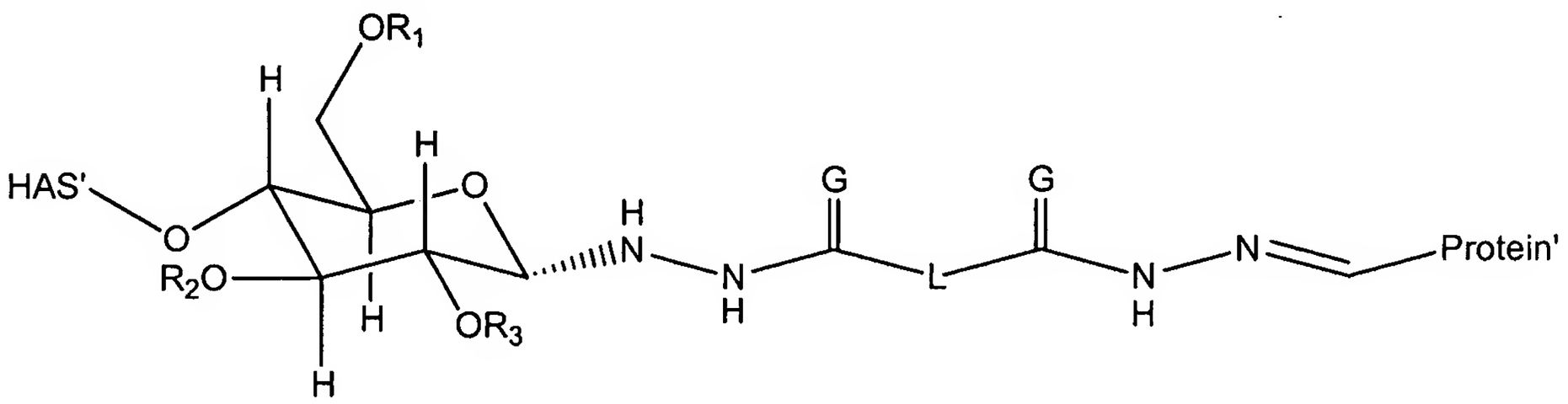
52. (Currently Amended) A conjugate [[as]] obtainable by [[a]] the method as claimed in ~~any of claims 1 to 51~~ claim 1.

53. (Currently Amended) The ~~conjugate~~ method as claimed in claim [[52]] 1, wherein A is a reactive carboxy group, and wherein A was introduced in the polymer whose reducing end was not oxidized, by reacting at least one hydroxy group of the polymer with a carbonic diester, and wherein[[,]] said ~~comprising~~ conjugate comprises one polymer molecule and at least one~~, in particular of from 1 to 10~~ protein ~~molecules~~ molecule linked to the polymer via amide linkages.

54. (Currently Amended) A conjugate comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula



and/or

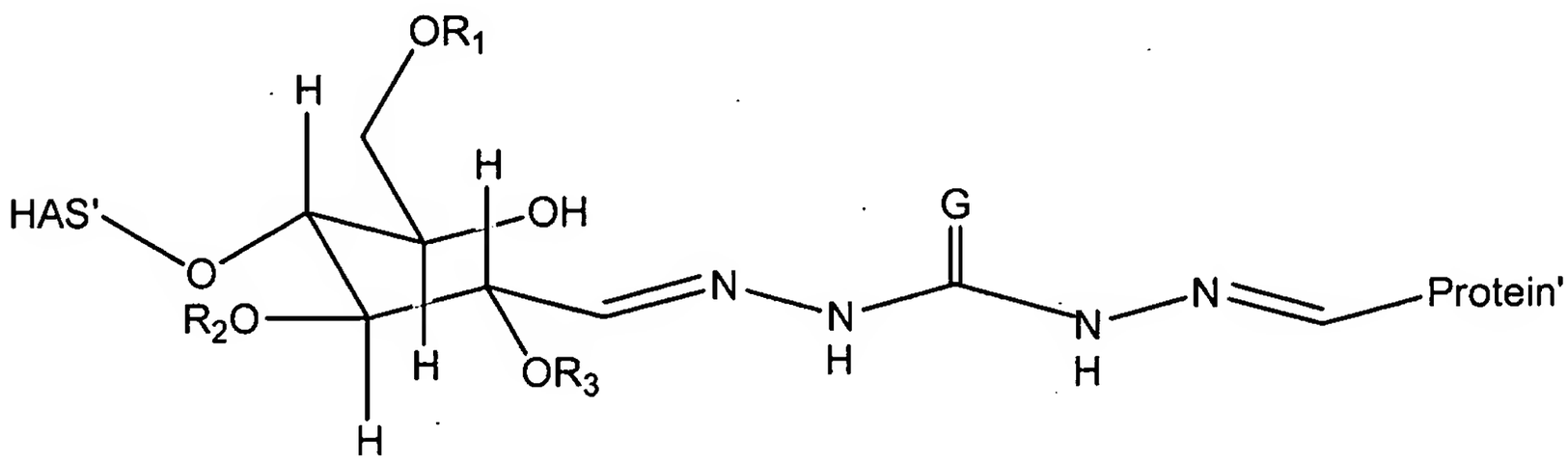


wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ wherein G is selected from the group consisting of O and S, ~~preferably O,~~ and wherein L is an optionally suitably substituted, linear, branched and/or cyclic hydrocarbon residue, optionally comprising at least one heteroatom~~,~~

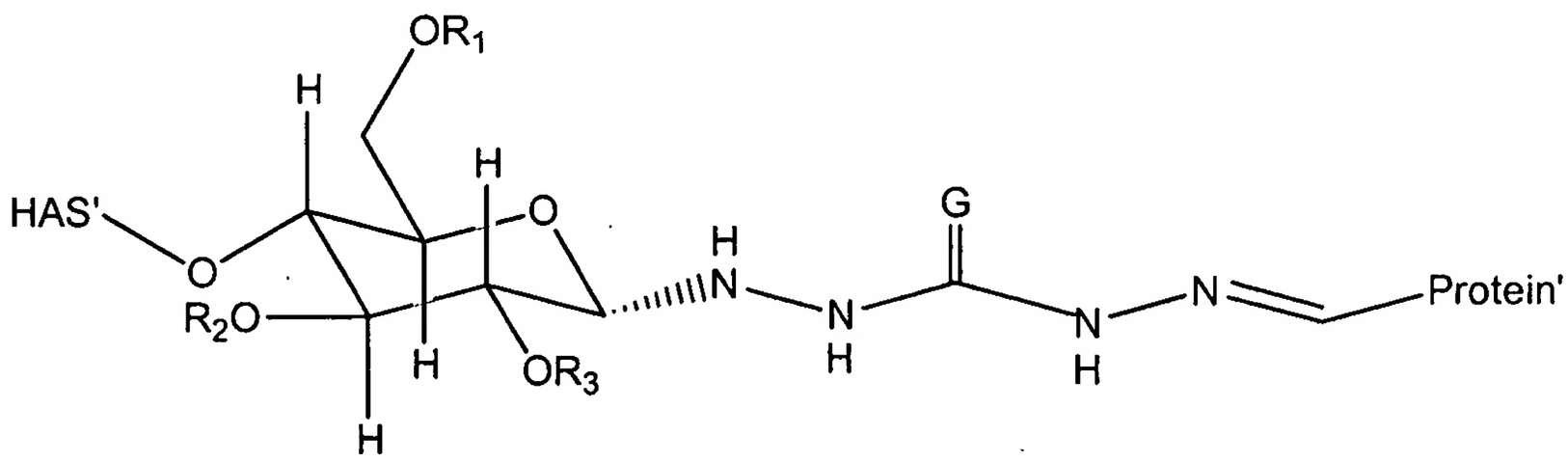
~~preferably an alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl residue~~ having from 2 to 60 carbon atoms.

55. (Currently Amended) The ~~conjugates~~ conjugate as claimed in claim 54,wherein -L- is $-(CH_2)_n-$ with n = 2, 3, 4, 5, 6, 7, 8, 9, or 10~~, preferably 2, 3, 4, 5, 6, more preferably 2, 3, 4, and especially preferably 4~~.

56. (Currently Amended) A conjugate comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula

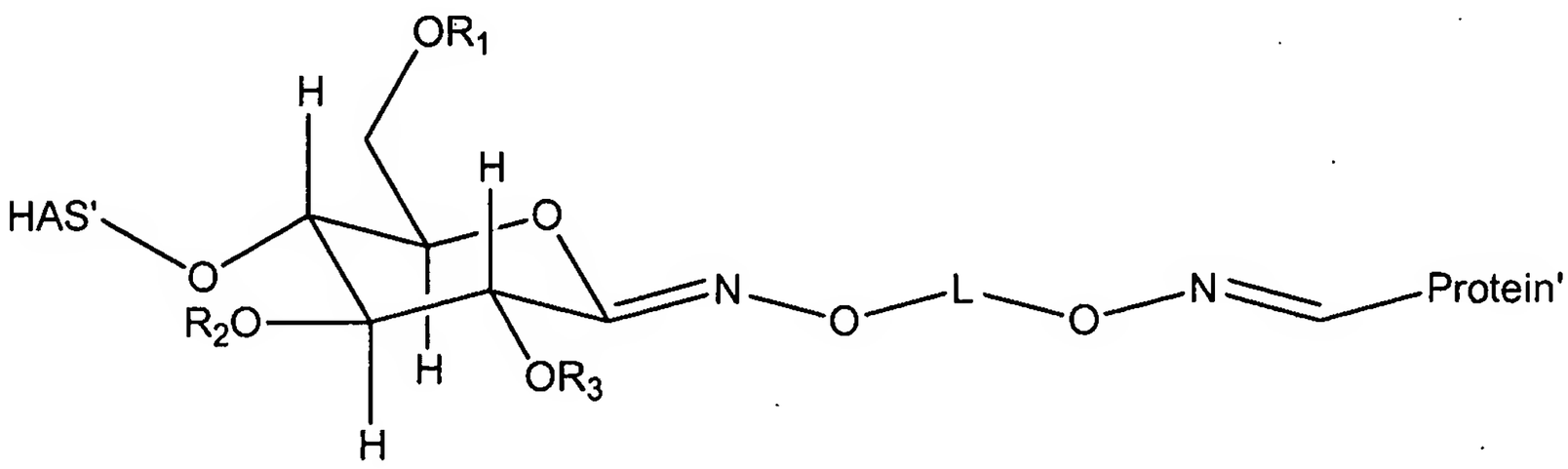


and/or

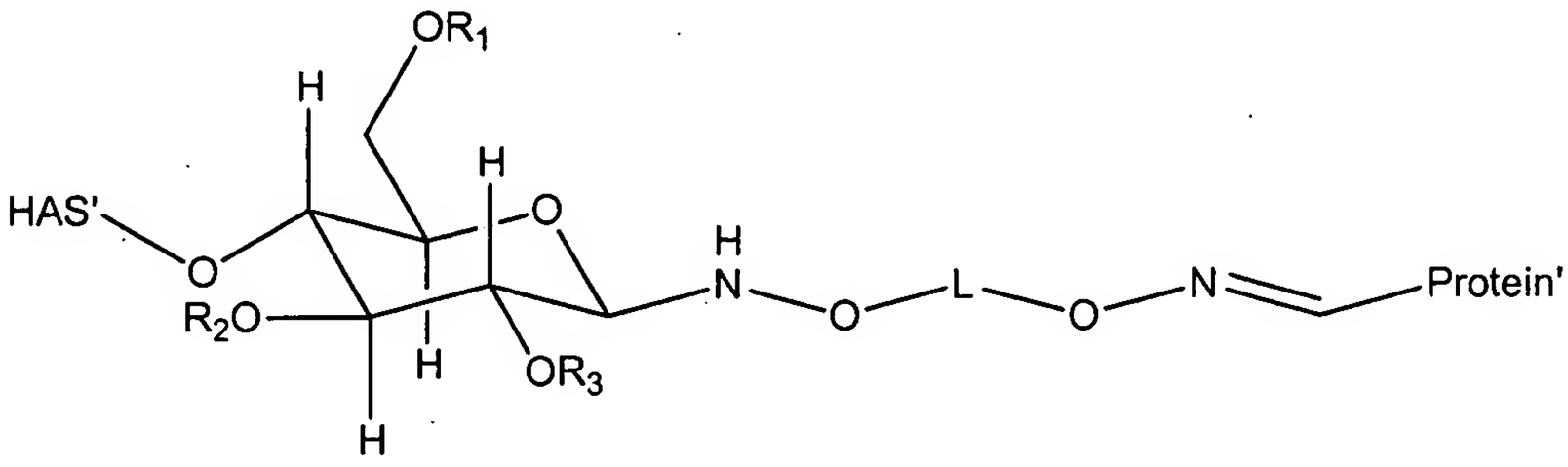


wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein G is selected from the group consisting of O and S~~, preferably O~~.

57. (Currently Amended) A conjugate comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula



and/or



wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 1 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein L is an optionally suitably substituted, linear, branched and/or cyclic hydrocarbon residue, optionally comprising at least one heteroatom~~, preferably an alkyl, aryl, aralkyl, heteroaryl,heteroaralkyl residue~~ having from 2 to 60 carbon atoms.

58. (Currently Amended) The conjugate as claimed in claim 57, wherein -L- is

$$-[(CR_aR_b)_mG]_n[CR_cR_d]_o-$$

wherein R_a, R_b, R_c, and R_d are independently hydrogen, alkyl, or aryl, ~~preferably hydrogen,~~ wherein G is selected from the group consisting of O and S, ~~preferably O,~~ and wherein

m 1, 2, 3 or 4, wherein the residues R_a and R_b may be the same or different in the m

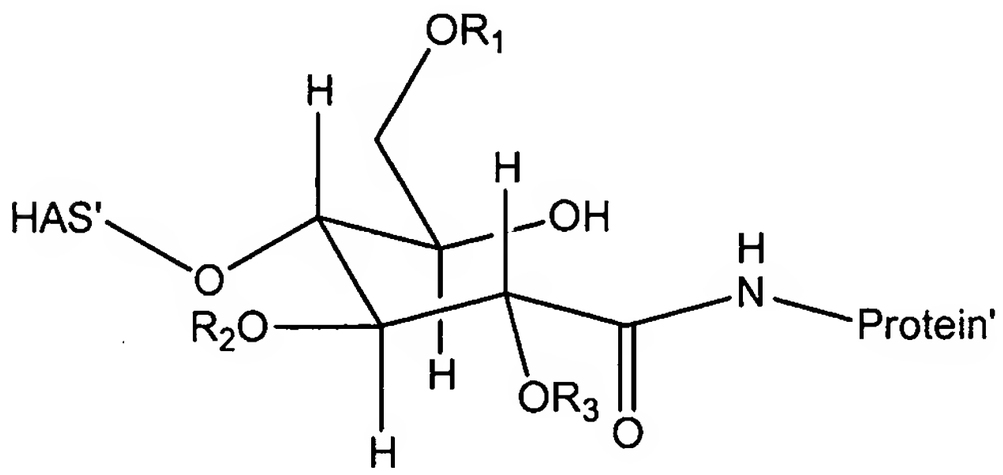
groups (CR_aR_b);

n 0 to 20~~, preferably 0 to 10, more preferably 1, 2, 3, 4, 5, most preferably 1 or 2~~;

o 0 to 20, ~~preferably 0 to 10, more preferably 1, 2, 3, 4, 5, most preferably 1 or 2,~~ wherein the residues R_c and R_d may be the same or different in the o groups (CR_cR_c)[[;]].

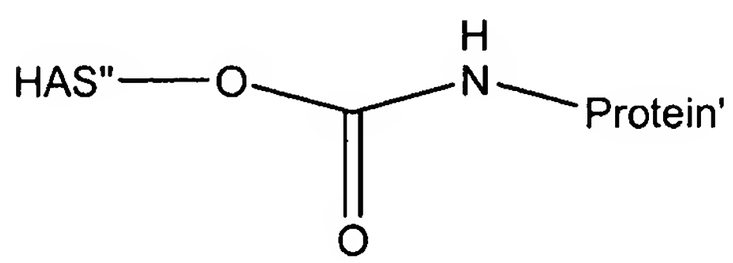
59. (Currently Amended) The conjugate as claimed in claim 57 ~~or 58~~, wherein R_a[[;]], R_b, R_c, and R_d are hydrogen, m = 2, n = 1, and o = 2.

60. (Currently Amended) A conjugate comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula



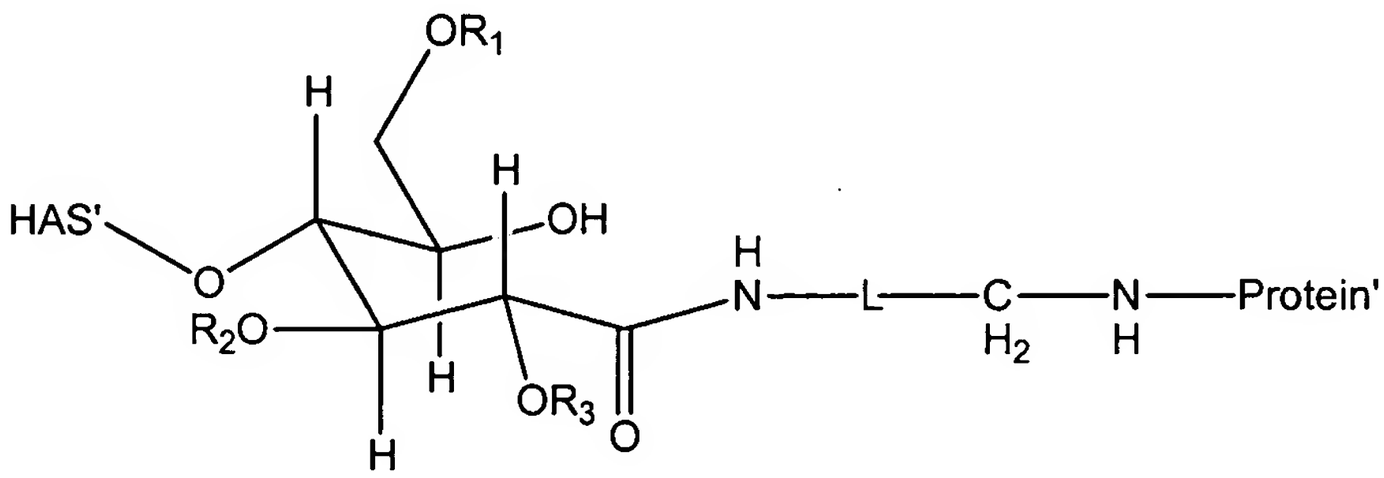
wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group~~.

61. (Currently Amended) A conjugate comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula

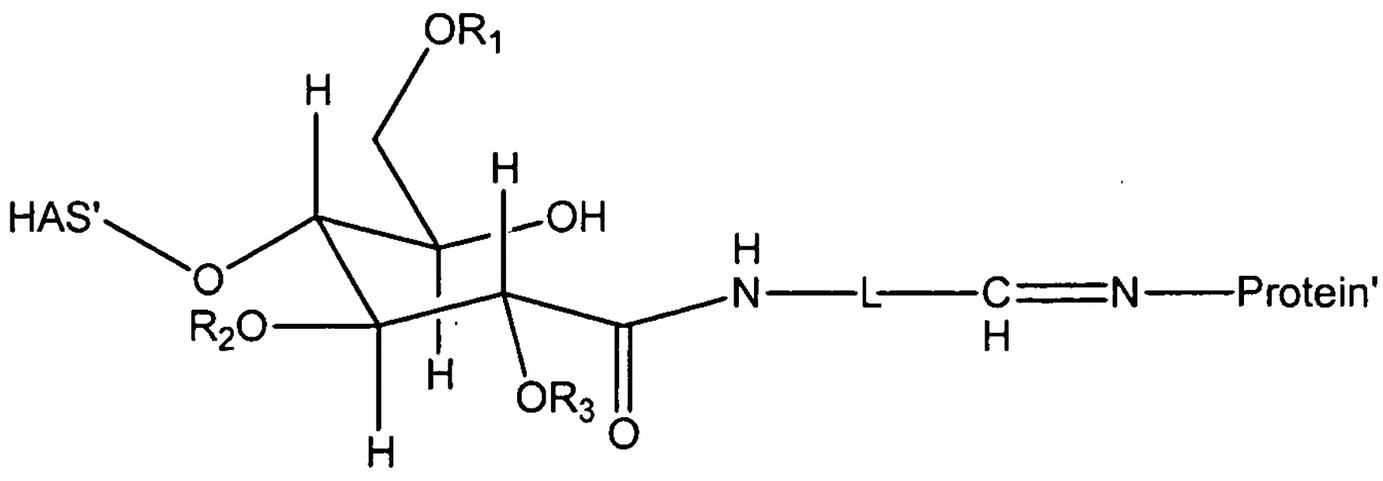


wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein the linkage -O-(C=O)- was formed by a reaction of a carboxy group or a reactive carboxy group with a hydroxy group of the HAS molecule, and wherein HAS" refers to the HAS molecule without said hydroxy group.

62. (Currently Amended) A conjugate, comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula



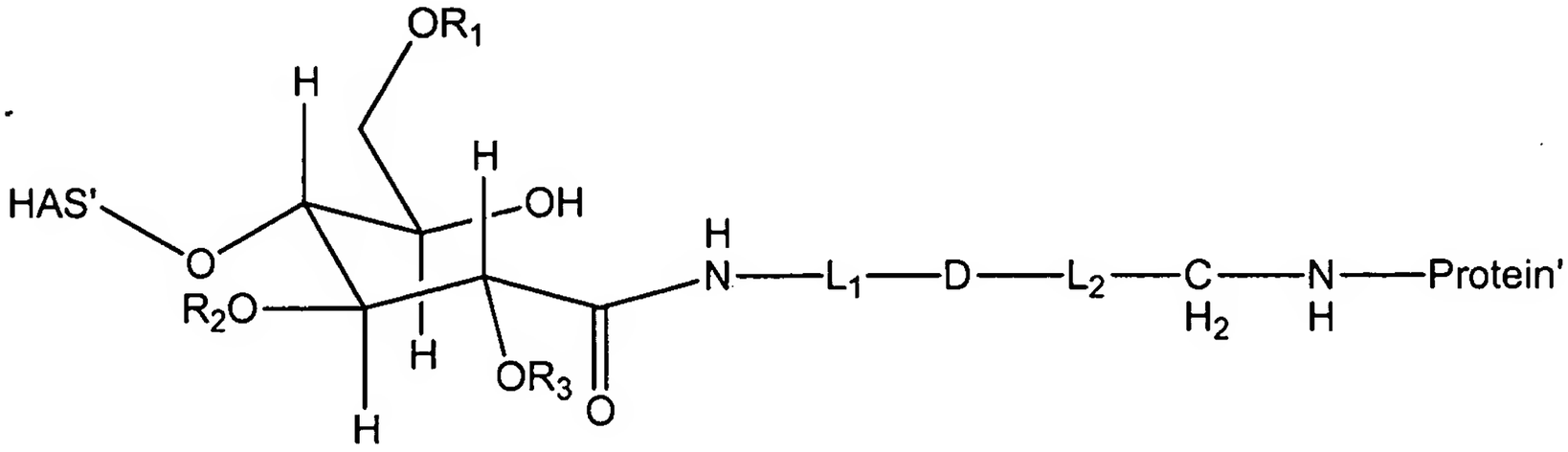
and/or



wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein L is an optionally substituted, linear, branched and/or cyclic hydrocarbon residue, optionally comprising at least one heteroatom, having from 1 to 60 ~~preferably from 1 to 40, more preferably from 1 to 20,~~

~~more preferably from 1 to 10, more preferably from 1 to 6 more preferably from 1 to 2~~ carbon atoms ~~and especially preferably 1 carbon atom, L being in particular CH2~~.

63. (Currently Amended) A conjugate, comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula



wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein L_1 and L_2 are independently an optionally substituted, linear, branched and/or cyclic hydrocarbon residue, optionally comprising at least one heteroatom, comprising an alkyl, aryl, aralkyl heteroalkyl, and/or heteroaralkyl moiety, said residue having from 1 to 60 ~~preferably from 1 to 40, more preferably from 1 to 20, more preferably from 1 to 10~~ carbon atoms, and wherein D is a linkage~~, preferably a covalent linkage which was~~ formed by a suitable functional group F_2 linked to L_1 and a suitable functional group F_3 linked to L_2.

64. (Currently Amended) The conjugate as claimed in claim 63, wherein L_1 is $-(CH_2)_n-$ with n = 2, 3, 4, 5, 6, 7, 8, 9, or 10~~, preferably 2, 3, 4, 5, 6, more preferably 2, 3, 4, and especially preferably 4~~.

65. (Currently Amended) The conjugate as claimed in claim 63 ~~or 64~~, wherein L_2 comprises an optionally suitably substituted aryl moiety~~, preferably an aryl moiety containing 6 carbon atoms, L_2 being especially preferably C_6H_4~~.

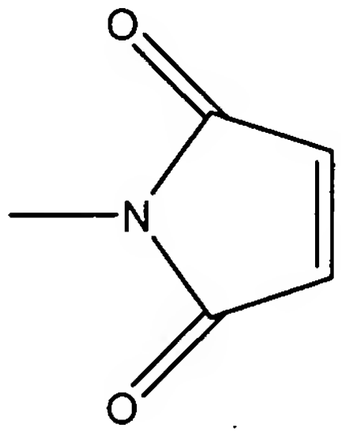
66. (Currently Amended) The conjugate as claimed in ~~any of claims 63 to 65~~ claim 63, wherein is F_2 selected from the group consisting of

- C-C-double bonds or C-C-triple bonds or aromatic C-C-bonds;
- ~~the~~ thiol ~~group~~ groups or ~~the~~ hydroxy groups;
- alkyl sulfonic acid hydrazide, aryl sulfonic acid hydrazide;
- 1,2-dioles;
- 1,2 amino-thioalcohols;
- azides;
- 1,2-aminoalcohols;
- the amino group $-NH_2$ or derivatives of the amino groups comprising the structure unit -NH- such as aminoalkyl groups, aminoaryl ~~group~~ groups, aminoaralkyl groups, or alkarlyamino groups;
- the hydroxylamino group $-O-NH_2$, or derivatives of the hydroxylamino group comprising the structure unit -O-NH-, such as hydroxylalkylamino groups, hydroxylarylamino groups, hydroxylaralkylamino groups, or hydroxalalkarylamino groups;
- alkoxyamino groups, aryloxyamino groups, aralkyloxyamino groups, or alkaryloxyamino groups, each comprising the structure unit -NH-O-;
- residues having a carbonyl group, -Q-C(=G)-M, wherein G is O or S, and M is~~,~~ ~~for example,~~
  - -OH or -SH;
  - an alkoxy group, an aryloxy group, an aralkyloxy group, or an alkaryloxy group;
  - an alkylthio group, an arylthio group, an aralkylthio group, or an alkarylthio group;
  - an alkylcarbonyloxy group, an arylcarbonyloxy group, an aralkylcarbonyloxy group, an alkarylcarbonyloxy group;
  - activated esters such as esters of hydroxylamines having imid structure such as N-hydroxysuccinimide or having a structure unit O-N where N is part of a heteroaryl compound or, with G = O and Q absent, such as

aryloxy compounds with a substituted aryl residue such as pentafluorophenyl, paranitrophenyl or trichlorophenyl;

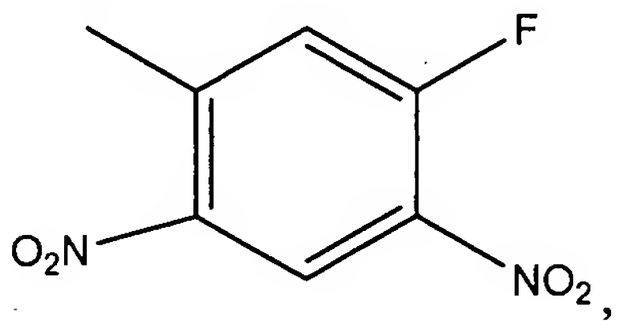
wherein Q is absent or NH or a heteroatom such as S or O;

- -NH-NH_2, or-NH-NH-;
- -NO_2;
- ~~the~~ nitril ~~group~~ groups;
- carbonyl groups such as the aldehyde group or the keto group;
- ~~the~~ carboxy group groups;
- ~~the~~ a -N=C=O group or ~~the~~ a -N=C=S group;
- vinyl halide groups such as ~~the~~ vinyl iodide or ~~the~~ vinyl bromide group or triflate;
- -C≡C-H;
- -(C=NH_2Cl)-OAlkyl
- groups -(C=O)-CH_2-Hal wherein Hal is Cl, Br, or I;
- -CH=CH-SO_2-;
- a disulfide group comprising the structure -S-S-;
- the group



;

- the group



and wherein F_3 is a functional group capable of forming a chemical linkage with F_2 ~~and is preferably selected from the above mentioned group, F_2 preferably comprising the moiety -NH-, more preferably comprising an amino group, F_3 preferably comprising the~~

~~moiety -(C=G)-, more preferably -(C=O)-, more preferably the moiety -(C=G)-G-, still more preferably -(C=O)-G-, and especially preferably -(C=O)-O, D being particularly preferably an amide linkage~~.

67. (Original) A conjugate, comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula

wherein the carbon atom of the moiety -CH_2-N_2- is derived from an aldehyde group which was introduced in the polymer by a ring-opening oxidation reaction, and wherein the nitrogen atom is derived from an amino group of the protein.

68. (Currently Amended) A conjugate, comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula

wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein L is an optionally substituted, linear, branched and/or cyclic hydrocarbon residue, optionally comprising at least one heteroatom, comprising an alkyl, aryl, aralkyl heteroalkyl, and/or heteroaralkyl moiety, said residue having from 2 to 60 ~~preferably from 2 to 40, more preferably from 2 to 20,~~

~~more preferably from 2 to 10~~ carbon atoms, and wherein the sulfur atom is derived from a cysteine residue or a disulfide group of the protein.

69. (Currently Amended) The conjugate as claimed in claim 68, wherein -L- is

$$-[(CR_aR_b)_mG]_n[CR_cR_d]_o-$$

wherein R_a[[;]], R_b, R_c, and R_d are independently hydrogen, alkyl, or aryl, ~~preferably hydrogen,~~ wherein G is selected from the group consisting of O and S, ~~preferably O,~~ and wherein

m 1, 2, 3 or 4, ~~most preferably 2,~~ wherein the residues R_a and R_b may be the same or different in the m groups (CR_aR_b);

n 1 to 20, ~~preferably 1 to 10, most preferably 1, 2, 3, or 4~~;

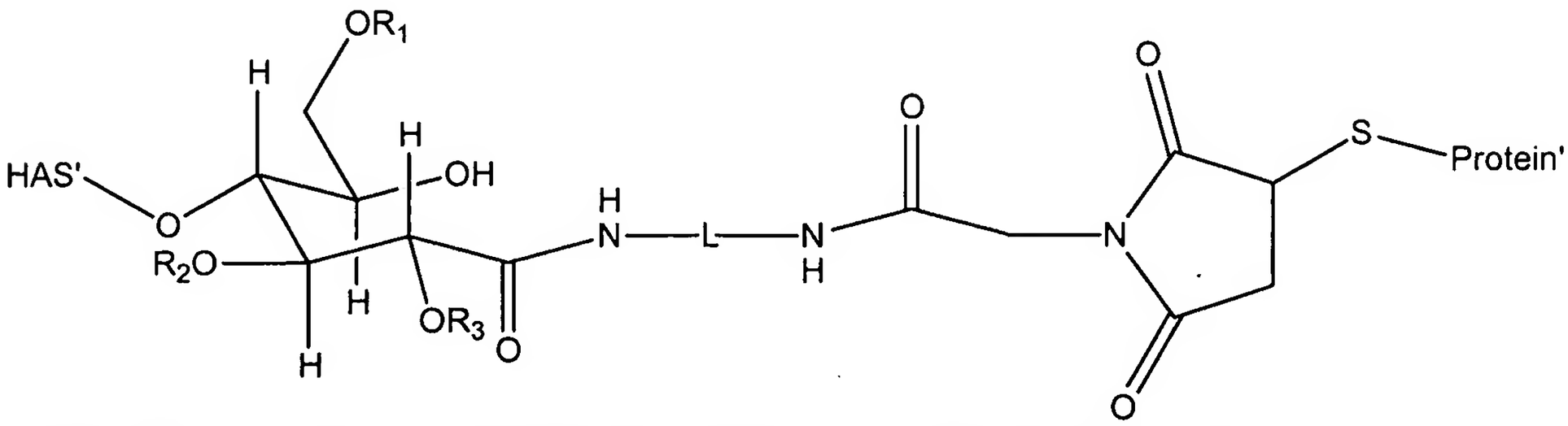
o 1 to 20, ~~preferably 1 to 10, more preferably 1, 2, 3, 4, 5, more preferably 1 or 2, most preferably 1,~~ wherein the residues R_c and R_d may be the same or different in the o groups (CR_cR_d);

or wherein

n 0, and

o 2 to 20, ~~preferably 2 to 10, more preferably 2, 3, 4, 5, 6, 7, or 8,~~ wherein the residues R_c and R_d may be the same or different in the o groups CR_cR_d.

70. (Currently Amended) A conjugate, comprising a protein and a polymer or a derivative thereof, wherein the polymer is a hydroxyalkyl starch (HAS) and the protein is a granulocyte colony stimulating factor (G-CSF), having a structure according to the formula



wherein R_1, R_2 and R_3 are independently hydrogen or a hydroxyalkyl group, a

hydroxyaryl group, a hydroxyaralkyl group or a hydroxyalkaryl group having of from 2 to 10 carbon atoms, ~~preferably hydrogen or a hydroxyalkyl group, more preferably hydrogen or a hydroxyethyl group,~~ and wherein L is an optionally substituted, linear, branched and/or cyclic hydrocarbon residue, optionally comprising at least one heteroatom, comprising an alkyl, aryl, aralkyl heteroalkyl, and/or heteroaralkyl moiety, said residue having from 2 to 60 ~~preferably from 2 to 40, more preferably from 2 to 20, more preferably from 2 to 10~~ carbon atoms, and wherein the sulfur atom is derived from a cysteine residue or a disulfide group of the protein.

71. (Currently Amended) The conjugate as claimed in claim 70, wherein -L- is

$$-[(CR_aR_b)_mG]_n[CR_cR_d]_o-$$

wherein R_a[[;]], R_b, R_c, <u>and</u> R_d are independently hydrogen, alkyl, <u>or</u> aryl, ~~preferably hydrogen,~~ wherein G is selected from the group consisting of O and S, ~~preferably O,~~ and wherein

m 1, 2, 3 or 4, ~~most preferably 2,~~ wherein the residues R_a and R_b may be the same or different in the m groups CR_aR_b;

n 1 to 20~~, preferably 1 to 10, most preferably 1,2, 3, or 4~~;

o 1 to 20, ~~preferably 1 to 10, more preferably 1, 2, 3, 4, 5, more preferably 1 or 2, most preferably 1,~~ wherein the residues R_c and R_d may be the same or different in the o groups CR_cR_d;

or wherein

n 0, and

o 2 to 20, ~~preferably 2 to 10, more preferably 2, 3, 4, 5, 6, 7, or 8,~~ wherein the residues R_c and R_d may be the same or different in the o groups CR_cR_d.

72. (Currently Amended) The conjugate as claimed in ~~any of claims 54 to 71~~ <u>claim 54</u>, wherein the hydroxyalkyl starch is hydroxyethyl starch.

73. (Currently Amended) The conjugate as claimed in claim 72 wherein the hydroxyethyl starch has a molecular weight of from 2 to 200 kD~~, preferably of from 4 to 130kD, more preferably of from 4 to 70kD~~.

74. (Canceled)

75. (Currently Amended) A pharmaceutical composition comprising in a therapeutically effective amount a conjugate as claimed in ~~any of claims 52 to 73~~ claim 54.

76. (Original) A pharmaceutical composition as claimed in claim 75, further comprising at least one pharmaceutically acceptable diluent, adjuvant, or carrier.

77. (Currently Amended) ~~Use of a conjugate as claimed in any of claims 52 to 73 for the preparation of a medicament~~ A method for ~~the~~ treatment of a disorder characterized by a reduced hematopoietic or immune function, comprising administering to a subject in need thereof a therapeutically effective amount of the conjugate as claimed in claim 54.

78. (Currently Amended) The ~~use~~ method as claimed in claim 77, wherein the disorder is a result of chemotherapy, radiation therapy, infectious disease, severe chronic neutropenia, or leukemia.